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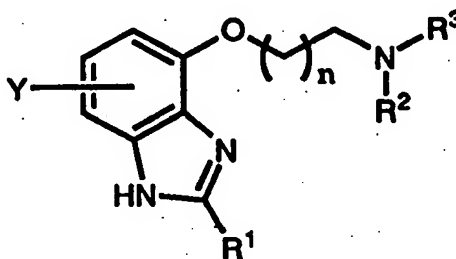
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US98/00613 <b>(22) International Filing Date:</b> 13 January 1998 (13.01.98) <b>(30) Priority Data:</b> 08/801,276 18 February 1997 (18.02.97) US <b>(71) Applicant:</b> AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0974 (US). <b>(72) Inventors:</b> NELSON, James, Albert; 7 Decision Way West, Washington Crossing, PA 18977 (US). MEWSHAW, Richard, Eric; 21 Boxwood Drive, Princeton, NJ 08540 (US). <b>(74) Agents:</b> ALICE, Ronald, W.; American Home Products Corporation, One Campus Drive, Parsippany, NJ 07054 (US) et al.	<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

**(54) Title:** 4-AMINOALKOXY-1H-BENZIMIDAZOLE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS DOPAMINE AUTORECEPTOR (D<sub>2</sub>) AGONISTS

**(57) Abstract**

This invention relates to D<sub>2</sub> dopaminergic compounds of formula (I), wherein R<sup>1</sup> is hydrogen, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, straight-chain or branched alkyl group having up to 6 carbons or benzyl optionally substituted by one to three substituents selected from halogen, amino, nitro, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy; R<sup>2</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl. R<sup>3</sup> is hydrogen, straight-chain or branched alkyl group having up to 10 carbon atoms, cyclohexylmethyl, -(CH<sub>2</sub>)<sub>m</sub>Ar, where Ar is phenyl, thienyl, furanyl, or pyridinyl, each optionally substituted by one to two substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkoxy, trifluoromethyl or C<sub>1</sub>-C<sub>6</sub> alkyl; or NR<sup>2</sup>R<sup>3</sup> is 1,2,3,4-tetrahydroquinolin-1-yl or 1,2,3,4-tetrahydroisoquinolin-2-yl; Y = halogen, lower alkyl, amino, and lower alkoxy; n = 1-5; or a pharmaceutically acceptable salt thereof. These D<sub>2</sub> dopaminergic compounds are useful in the treatment of schizophrenia, Parkinson's disease, Tourette's syndrome, and drug or alcohol addiction.



(I)

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4-AMINOALKOXY-1H-BENZIMIDAZOLE DERIVATIVES, THEIR PREPARATION AND  
THEIR USE AS DOPAMINE AUTORECEPTOR (D<sub>2</sub>) AGONISTS

5 FIELD OF INVENTION

This invention relates to 4-(aminoalkoxy)-1H-benzimidazoles which have dopamine D<sub>2</sub> agonist activity and thus are useful in the treatment of schizophrenia, Parkinson's disease, Tourette's syndrome and drug or alcohol addiction.

10

BACKGROUND OF THE INVENTION

Efforts to induce antipsychotic activity with dopamine autoreceptor agonists have been successful (Dorsini *I Adv. Biochem. Psychopharmacol.*, **16**, 645-648, 1977; Tamminga *et al.*, *Science*, **200**, 567-568, 1975; and Tamminga *et al.*, *Psychiatry*, 398-402, 1986). A method for determining intrinsic activity at the dopamine D<sub>2</sub> receptor was recently reported (Lahti *et al.*, *Mol. Pharm.*, **42**, 432-438, 1993) Intrinsic activity is predicted using the ratio of the "low-affinity agonist" (LowAg) state of the receptor and the "high-affinity agonist" (HighAg) state of the receptor, i.e. LowAg/HighAg. These ratios correlate with the agonist, partial agonist, and antagonist activities of a given compound, which activities characterize a compounds ability to elicit an antipsychotic effect.

20

In accordance with this invention, there is provided a group of compounds which are useful antipsychotic agents. The compounds of this invention are dopamine agonists various degrees of intrinsic activity some of which are selective autoreceptor agonists, and therefore partial agonist (i.e. activate only autoreceptors versus postsynaptic D<sub>2</sub> dopamine receptors). As such, they provide functional modulation of the dopamine systems of the brain without the excessive blockade of the postsynaptic dopamine receptors which have been observed to be responsible for the serious side effects frequently exhibited by agents found otherwise clinically effective for the treatment of schizophrenia. Activation of the dopamine autoreceptors results in reduced neuronal firing as well as inhibition of dopamine synthesis and release and therefore provide a means of controlling hyperactivity of the dopaminergic systems. The compounds of this invention were also found to have high intrinsic activity and therefore they can behave as the natural neurotransmitter i.e. as full agonists. As such, they are useful in the treatment of diseases having abnormal concentrations of dopamine could be used as dopamine surrogates possibly in the treatment of Parkinson's disease. The compounds of this invention are essentially free from extrapyramidal side effects (EPS).

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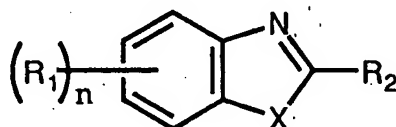
## DESCRIPTION OF THE PRIOR ART

A number of compounds structurally related to the compounds of this invention are claimed in prior art.

5

JP 02306916A claims a class of benzazole compounds of the formula below, where

X is



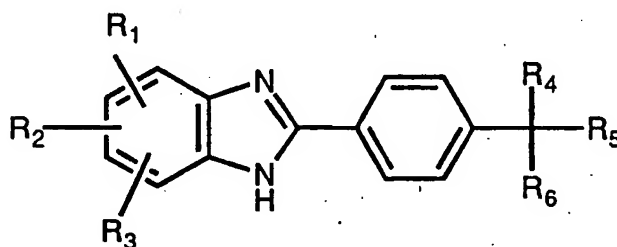
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S or N, which are inhibitors of platelet adhesion for the treatment of arteriosclerosis, ischemic heart diseases, chronic arterial obstruction, and acute or chronic nephritis. In the above formula,  $R_1$  includes  $-(O-A)_m-NR^4R^5$  where A is lower alkylene, m is 0 or 1,  $R^4$  and  $R^5$  include hydrogen, phenyl(lower)alkyl, or  $NR^4R^5$  is a 5-6 membered saturated or unsaturated heterocycle and  $R_2$  includes phenyl optionally substituted by 1-3 substituents selected from optionally halogenated lower alkoxy, lower alkyl, hydroxy, halogen or aminoalkoxy.

15

DE 3830060 claims a class of 2-Arylbenzimidazole erythrocyte aggregation inhibiting compounds of the following formula

20



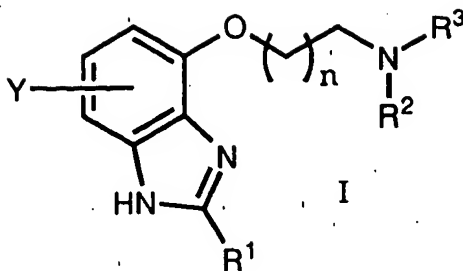
where  $R^4$  is methyl, cyano, carboxamido or aminomethyl,  $R^5$  is H or alkyl,  $R^6$  is alkyl or cycloalkyl or  $R^5$  and  $R^6$  completes a cyclohexane ring which are useful for the treatment of circulatory disorders and shock.

25

## SUMMARY OF THE INVENTION

The compounds of this invention are depicted by the following Formula I:

30



wherein:

R<sup>1</sup> is hydrogen, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, straight-chain or branched alkyl group having up to 6 carbons or benzyl optionally substituted by one to three substituents selected from halogen, amino, nitro, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy;

R<sup>2</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl.

R<sup>3</sup> is hydrogen, straight-chain or branched alkyl group having up to 10 carbon atoms, cyclohexylmethyl, -(CH<sub>2</sub>)<sub>m</sub>Ar where Ar is phenyl, thienyl, furanyl, or pyridinyl, each optionally substituted by one to two substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkoxy, trifluoromethyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

or NR<sup>2</sup>R<sup>3</sup> is 1,2,3,4-tetrahydroquinolin-1-yl or 1,2,3,4-tetrahydroisoquinolin-2-yl;

Y = halogen, lower alkyl, amino, and lower alkoxy;

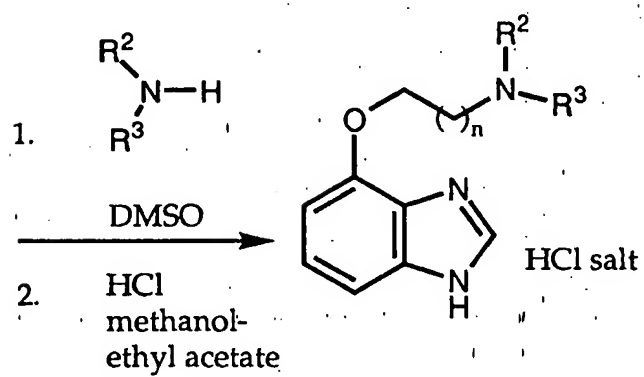
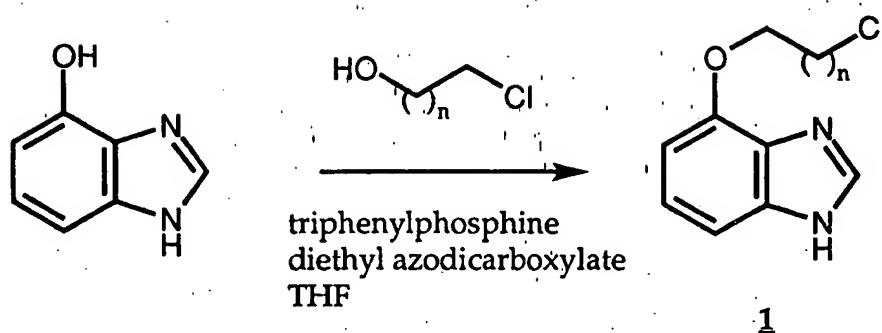
n = 1-5;

and the pharmaceutically acceptable salts thereof.

The pharmaceutically acceptable acid addition salt having the utility of the free base are prepared by methods well known to the art with both inorganic or organic acids, including but not limited to fumaric, maleic, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene-sulfonic, hydrochloric hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

The compounds of Formula III, where R<sup>1</sup> is hydrogen, can be prepared by the overall sequence as follows:

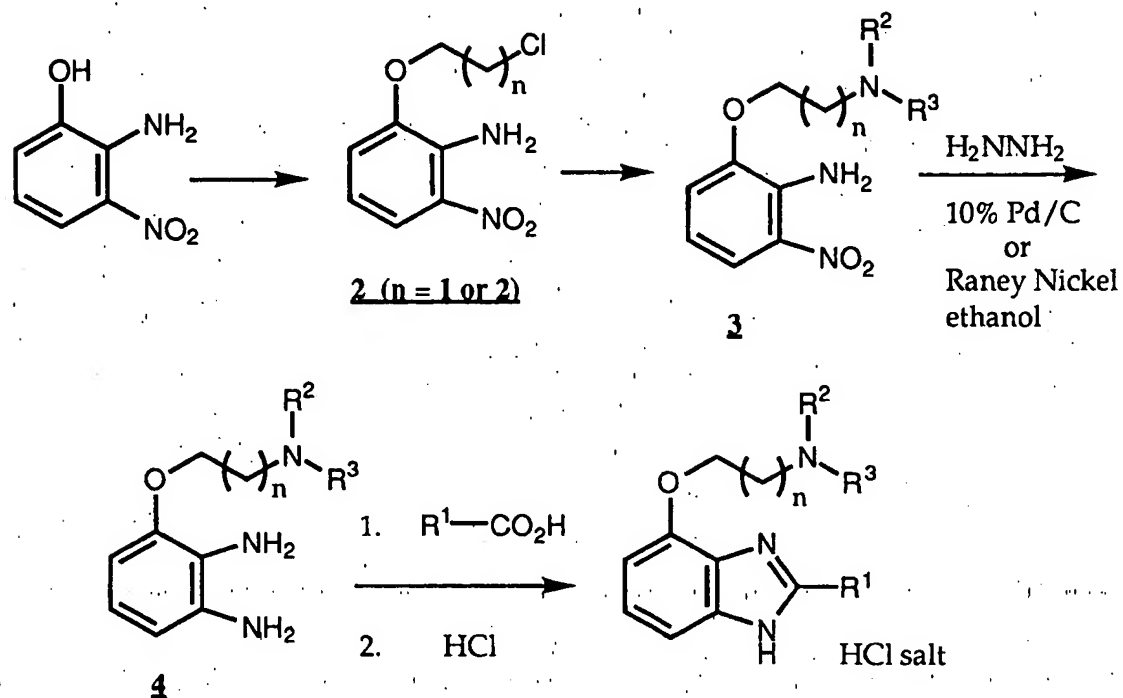
## Scheme I



The compounds of Formula III, where R<sub>1</sub> is not hydrogen, can be prepared by the overall sequence as follows:

## Scheme II

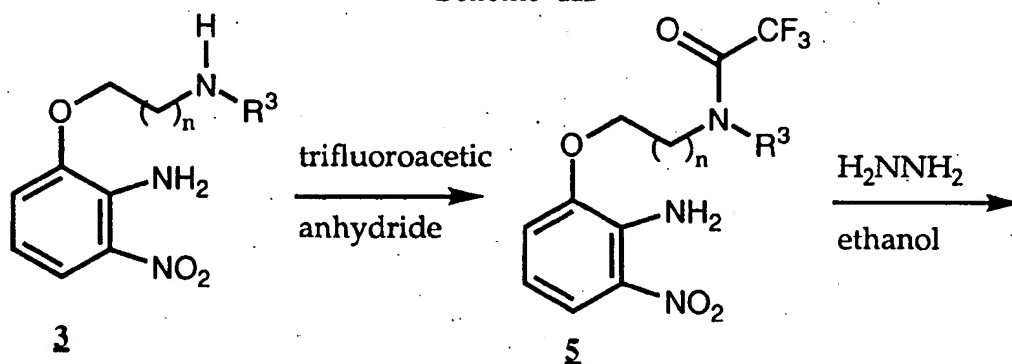
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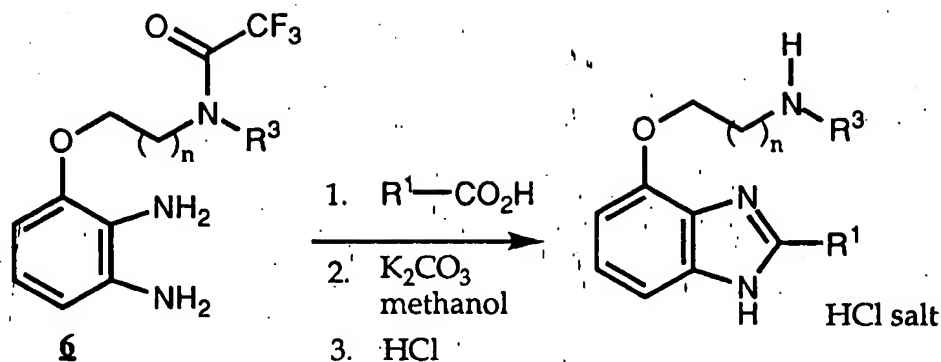
The compounds of Formula III, where R<sub>2</sub> is hydrogen; the secondary amine can be protected by a trifluoroacetyl group prepared by the overall sequence as follows:

10

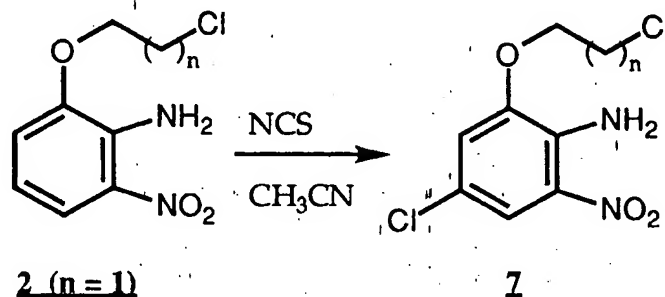
## Scheme III







An intermediate for compounds of Formula III where Y is halogen can be prepared  
 5 by the following sequence:



10 Specific exemplification of the production of representative compounds of this  
 invention is given in the following procedures:

#### Intermediate 1

#### 4-(2-Chloroethoxy)-benzimidazole

To a solution of 4-hydroxybenzimidazole (3.1 g, 32.4 mmol), triphenylphosphine  
 (12.75 g, 48.6 mmol) and 2-chloroethanol (5.2 g, 64.8 mmol) in tetrahydrofuran (75 mL)  
 20 at 0 - 5 °C was added over 30 min a solution of diethyl azodicarboxylate (8.5 g, 48.7  
 mmol) in tetrahydrofuran (75 mL). The mixture was warmed to 23° C and stirred for 48  
 hr. The solvent was removed under vacuum to give a dark brown oil. Purification by  
 chromatography (silica gel, ethyl acetate-1% 2M NH<sub>3</sub> in methanol) afforded 2.9 g (63.8%)  
 of a solid residue that was recrystallized from ethyl acetate to give the title compound as a  
 25 white solid, mp 153-154 °C.

Elemental analysis for  $C_9H_9ClN_2O$ :

Calc'd: C, 54.97; H, 4.61; N, 14.25

Found: C, 54.86; H, 4.38; N, 14.26

5

Intermediate 2a (n=1)

**2-(2-Chloro-ethoxy)-6-nitro-phenylamine**

10 A slurry containing 2-amino-3-nitrophenol (32.0 g, 0.208 mol), 1,2-dichloroethane (260.0 g, 2.65 mol), potassium carbonate (35.0 g, 0.252 mol) and 2-butanone (750 mL) was refluxed for 24 hr. The mixture was cooled, filtered and the solids were washed with ethyl acetate. The filtrate was concentrated to an oily residue that was dissolved in ethyl acetate (500 mL). The organic layer was washed with 1 N sodium hydroxide (250 mL),  
15 water (500 mL), and brine (2X 500 mL), dried over anhydrous magnesium sulfate. Concentration of the filtered solution and trituration of the residue with hexane afforded 37.8 g (84.6%) of product as an orange solid, mp 71-73 °C; MS (+)PBEI *m/e* 216/218 ( $M^+$ ).

20 Elemental analysis for  $C_8H_9ClN_2O_3$ :  
Calc'd: C, 44.36; H, 4.19; N, 12.93  
Found: C, 44.45; H, 4.02; N, 12.97

25 Following this general procedure above utilizing 1,3-dibromopropane afforded intermediate 2b, 2-(3-bromo-propoxy)-6-nitro-phenylamine, as a yellow solid, (78.7%) mp 88-89 °C; MS EI *m/e* 274/276 [ $M^+$ ].

30 Elemental analysis for  $C_9H_{11}BrN_2O_3$ :  
Calc'd: C, 39.29; H, 4.03; N, 10.18  
Found: C, 39.71; H, 3.91; N, 10.27

## Intermediate 3a

**2-(2-Benzylamino-ethoxy)-6-nitro-phenylamine**

5 A mixture of 2-(2-chloroethoxy)-6-nitro-phenylamine (2a, 3.0 g, 13.8 mmol) and benzylamine (9.0 g, 84.0 mmol) was heated at 100–110° C for 6 hr. The excess benzylamine was removed by distillation under vacuum (70 - 75° C / 0.1 mm). The residue was poured into 1 N sodium hydroxide (300 mL) and extracted with ethyl acetate (2X, 300 mL). The combined organic layer was washed with water (2X, 300 mL) and brine (300 mL). The ethyl acetate layer was dried over anhydrous magnesium sulfate, filtered, and the solvent removed under vacuum to give 5.1 g of crude red oil. Purification by chromatography (500 g silica gel, ethyl acetate : 2 M NH<sub>3</sub> in methanol, 20 : 1 ) afforded 3.54 g (89.3%) of a red semi-solid, mp 33-60 °C; MS EI *m/e* 287 (M<sup>+</sup>).

15 Elemental analysis for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>:

Calc'd: C, 62.71; H, 5.96; N, 14.62

Found: C, 62.64; H, 6.04; N, 14.23

20 This general procedure utilizing 4-methyl-benzylamine, thiophene-2-methylamine, 1-naphthalenemethylamine, 1,2,3,4-tetrahydroisoquinoline afforded:

3b 2-[2-(4-Methyl-benzylamino)-ethoxy]-6-nitro-phenylamine as a yellow solid (89.0 %): mp 55-57 °C; MS EI *m/e* 301 (M<sup>+</sup>).

25

Elemental analysis for C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>:

Calc'd: C, 63.77; H, 6.36; N, 13.94

Found: C, 63.32; H, 6.37; N, 13.82

30 3c 2-Nitro-6-[2-[(thiophen-2-ylmethyl)-amino]-ethoxy]-phenylamine as a red semi-solid material (88.5%).

Elemental analysis for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>S:

Calc'd: C, 53.23; H, 5.15; N, 14.32

35 Found: C, 52.86; H, 4.93; N, 14.15

3d 2-{2-[(Naphthalen-1-ylmethyl)-amino]-ethoxy}-6-nitro-phenylamine as a yellow solid (76.3 %), mp 66-67 °C; MS EI *m/e* 337(M<sup>+</sup>).

Elemental analysis for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>:

Calc'd: C, 67.64; H, 5.68; N, 12.45

Found: C, 67.20; H, 5.66; N, 12.26

5

3e 2-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-ethoxy]-6-nitro-phenylamine as a yellow solid (87.1%), mp 95-96 °C; MS EI *m/e* 313 (M<sup>+</sup>).

Elemental analysis for C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>:

10

Calc'd: C, 65.16; H, 6.11; N, 13.41

Found: C, 64.87; H, 6.11; N, 13.40

This general procedure utilizing 2-(3-bromo-propoxy)-6-nitro-phenylamine (2b, n=2) and benzylamine afforded:

15

3f 2-(3-Benzylamino-propoxy)-6-nitro-phenylamine as a viscous orange oil (85.5 %); MS EI *m/e* 301 (M<sup>+</sup>).

Elemental analysis for C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>:

20

Calc'd: C, 63.77; H, 6.36; N, 13.94

Found: C, 63.66; H, 6.28; N, 13.89

This general procedure utilizing 4-chloro-2-(2-chloro-ethoxy)-6-nitro-phenylamine (7) and benzylamine, 4-chloro-benzylamine afforded:

25

3g 2-(2-Benzylamino-ethoxy)-4-chloro-6-nitro-phenylamine as a orange-brown colored solid (54.0 %), mp 87-88 °C; MS EI *m/e* 321/323 (M<sup>+</sup>).

Elemental analysis for C<sub>15</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>3</sub>:

30

Calc'd: C, 55.99; H, 5.01; N, 13.06

Found: C, 55.85; H, 4.90; N, 13.13

3h 2-[2-(4-Chloro-benzylamino)-ethoxy]-4-chloro-6-nitro-phenylamine as an orange-brown colored solid (83.0 %), mp 116-118 °C.

35

Elemental analysis for C<sub>13</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>:

Calc'd: C, 50.58; H, 4.24; N, 11.80

Found: C, 50.65; H, 4.13; N, 11.51

3i 2-[2-(4-Fluoro-benzylamino)-ethoxy]-6-nitro-phenylamine as an orange solid (89.8 %), mp 72-74 °C.

Elemental analysis for C<sub>15</sub>H<sub>16</sub>FN<sub>3</sub>O<sub>3</sub>:

Calc'd: C, 59.01; H, 5.28; N, 13.76

Found: C, 58.92; H, 5.16; N, 13.71

3j 2-Nitro-6-[2-(4-trifluoromethyl-benzylamino)-ethoxy]-phenylamine as an orange solid (86.7 %), mp 64-66 °C.

Elemental analysis for C<sub>16</sub>H<sub>16</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>:

Calc'd: C, 54.09; H, 4.54; N, 11.83

Found: C, 53.99; H, 4.33; N, 11.74

3k 2-Nitro-6-[2-(3-phenyl-propylamino)-ethoxy]-phenylamine quarter hydrate as a viscous orange oil (83.4 %); MS EI m/e 315 (M<sup>+</sup>)

Elemental analysis for C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub> · 0.25 H<sub>2</sub>O:

Calc'd: C, 63.83; H, 6.78; N, 13.14

Found: C, 63.90; H, 6.56; N, 13.07

#### Intermediate 4a

#### 3-(2-Benzylamino-ethoxy)-benzene-1,2-diamine

To a mixture containing 2-(2-benzylamino-ethoxy)-6-nitro-phenylamine (3a, 0.5 g, 1.74 mmol), 10% palladium on carbon (0.1 g) in ethanol (20 mL) was slowly added a solution of hydrazine hydrate (0.6 mL) in ethanol (6.0 mL). The mixture was heated to 55-60 °C and stirred at that temperature for 16 hr. The mixture was cooled to 25 °C, filtered and the catalyst was washed with ethanol. The filtrate was concentrated under vacuum and the residue was diluted with ethyl acetate (100 mL). The organic layer was washed with water (2X, 100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent removed under vacuum to give 0.38 g (85.5% crude yield) of product as a brown viscous oil. This material was not purified further, but used immediately in the next step.

This general procedure utilizing 2-[2-(4-methyl-benzylamino)-ethoxy]-6-nitro-phenylamine (3b), 2-nitro-6-[2-[(thiophen-2-ylmethyl)-amino]-ethoxy]-phenylamine (3c), 2-[2-[(naphthalen-1-ylmethyl)-amino]-ethoxy]-6-nitro-phenylamine (3d), 2-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethoxy]-6-nitro-phenylamine (3e), and 2-(3-benzylamino-propoxy)-6-nitro-phenylamine (3f) afforded:

4b 3-[2-(4-Methyl-benzylamino)-ethoxy]-benzene-1,2-diamine as a off-white solid (79.4 %), mp 77-79 °C; MS EI *m/e* 271 ( $M^+$ ).

10 Elemental analysis for  $C_{16}H_{21}N_3O$ :

Calc'd: C, 70.82; H, 7.80; N, 15.49

Found: C, 70.53; H, 7.89; N, 15.50

4c 3-[2-[(Thiophen-2-ylmethyl)-amino]-ethoxy]-benzene-1,2-diamine as an amber-colored oil (70.0 %); MS EI *m/e* 263 ( $M^+$ ).

4d 3-[2-[(Naphthalen-1-ylmethyl)-amino]-ethoxy]-benzene-1,2-diamine quarterhydrate as a black oil (82.0 %); MS EI *m/e* 307 ( $M^+$ ).

20 Elemental analysis for  $C_{19}H_{21}N_3O \cdot 0.25 H_2O$ :

Calc'd: C, 73.17; H, 6.95; N, 13.47

Found: C, 73.29; H, 6.86; N, 13.30

4e 3-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-ethoxy]-benzene-1,2-diamine as a solid (95 %), mp 76-77 °C. This material was characterized as the dihydrochloride  $0.4 H_2O$  salt; MS EI *m/e* 283 ( $M^+$ ).

Elemental analysis for  $C_{17}H_{21}N_3O \cdot 2 HCl \cdot 0.4 H_2O$ :

Calc'd: C, 56.17; H, 6.60; N, 11.56

30 Found: C, 56.15; H, 6.68; N, 11.25

4f 3-(3-Benzylamino-propoxy)-benzene-1,2-diamine as an amber-colored oil; MS EI *m/e* 271 ( $M^+$ ).

35 Elemental analysis for  $C_{16}H_{21}N_3O \cdot 0.3 H_2O$ :

Calc'd: C, 69.44; H, 7.87; N, 15.18

Found: C, 69.47; H, 7.82; N, 15.30

This general procedure utilizing 2-[2-(4-chloro-benzylamino)-ethoxy]-4-chloro-6-nitro-phenylamine (3h) and Raney nickel in place of 10 % Pd/C afforded:

5    4g    3-[2-(4-chloro-benzylamino)-ethoxy]-4-chloro-benzene-1,2-diamine as a light-tan colored solid (75.0 %), mp 109-110 °C.

Elemental analysis for C<sub>15</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>O:

Calc'd: C, 55.23; H, 5.25; N, 12.88

10    Found: C, 55.04; H, 5.09; N, 12.62

4h    3-[2-(4-Fluoro-benzylamino)-ethoxy]-benzene-1,2-diamine as a white solid (82.4 %), mp 70-71 °C.

15    Elemental analysis for C<sub>15</sub>H<sub>18</sub>FN<sub>3</sub>O · 0.1H<sub>2</sub>O:

Calc'd: C, 65.12; H, 6.62; N, 15.16

Found: C, 64.94; H, 6.52; N, 14.93

20    4i    3-[2-(4-Trifluoromethyl-benzylamino)-ethoxy]-benzene-1,2-diamine as a white solid (87.2 %), mp 94-95 °C.

Elemental analysis for C<sub>16</sub>H<sub>18</sub>F<sub>3</sub>N<sub>3</sub>O:

Calc'd: C, 59.07; H, 5.58; N, 12.92

Found: C, 58.93; H, 5.24; N, 12.78

25

4j    3-[2-(3-phenyl-propylamino)-ethoxy]-benzene-1,2-diamine as an oil (76.2 %); MS (+)FAB m/e 286 (M+H<sup>+</sup>).

#### Intermediate 5a

30

#### N-[2-(2-Amino-3-nitro-phenoxy)-ethyl]-N-benzyl-2,2,2-trifluoro-acetamide

35    To a solution containing 2-(2-benzylamino-ethoxy)-6-nitro-phenylamine (3a, 0.50 g, 1.74 mmol), triethylamine (0.50 mL) and methylene chloride (10 mL) was slowly added trifluoroacetic acid anhydride (0.32 mL, 2.26 mmol). After 2 hr, the reaction mixture was poured into 1 N sodium hydroxide (50 mL) and extracted with methylene chloride. The

organic layer was washed with water (2X, 50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent removed under vacuum to give a crude yellow residue. Crystallization of this material from ethyl acetate-hexane afforded 0.55 g (81.7 %) of a yellow solid, mp 134-135 °C; MS EI *m/e* 383 (M<sup>+</sup>).

Elemental analysis for C<sub>17</sub>H<sub>16</sub>F<sub>3</sub>N<sub>3</sub>O<sub>4</sub>:

Calc'd: C, 53.27; H, 4.21; N, 10.96

Found: C, 53.09; H, 4.35; N, 10.93

This general procedure utilizing 2-(2-benzylamino-ethoxy)-4-chloro-6-nitro-phenylamine (3g) afforded:

**5b** N-[2-(2-Amino-5-chloro-3-nitro-phenoxy)-ethyl]-N-benzyl-2,2,2-trifluoro-acetamide as a yellow solid (76.9 %), mp 106-108 °C; MS (+)FAB *m/e* 418/420 (M+H)<sup>+</sup>.

Elemental analysis for C<sub>17</sub>H<sub>15</sub>ClF<sub>3</sub>N<sub>3</sub>O<sub>4</sub>:

Calc'd: C, 48.88; H, 3.62; N, 10.06

Found: C, 48.96; H, 3.50; N, 10.03

#### Intermediate 6a

#### N-[2-(1,2-Diamino-benzene-3-yloxy)-ethyl]-N-benzyl-2,2,2-trifluoro-acetamide

To a mixture containing N-[2-(2-amino-3-nitro-phenoxy)-ethyl]-N-benzyl-2,2,2-trifluoro-acetamide (**5a**, 0.4 g, 1.04 mmol), 10% palladium on carbon (0.1 g) in ethanol (30 mL) was slowly added a solution of hydrazine hydrate (0.6 mL) in ethanol (10.0 mL). The mixture was heated to 55-60 °C and stirred at that temperature for 1 hr. The mixture was cooled to 25 °C, filtered and the catalyst was washed with ethanol. The filtrate was concentrated under vacuum and the residue was diluted with ethyl acetate (100 mL). The organic layer was washed with water (2X, 100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent removed under vacuum to give 0.32 g (87.5% crude yield) of product as a brown viscous oil; MS (+)FAB *m/e* 354 (M+H)<sup>+</sup>.



This general procedure utilizing N-[2-(2-amino-5-chloro-3-nitro-phenoxy)-ethyl]-N-benzyl-2,2,2-trifluoro-acetamide (**5b**) afforded:

**6b** N-Benzyl-N-[2-(2,3-diamino-5-chloro-phenoxy)-ethyl]-2,2,2-trifluoro-acetamide as a brown viscous oil (91.3 %); MS EI *m/e* 387/389 ( $M^+$ ).

Elemental analysis for  $C_{17}H_{11}ClF_3N_3O_2$ :

Calc'd: C, 52.65; H, 4.42; N, 10.84

Found: C, 52.47; H, 4.39; N, 10.90

#### Intermediate 7

#### 4-Chloro-2-(2-chloro-ethoxy)-6-nitro-phenylamine

A solution of 2-(2-chloro-ethoxy)-6-nitro-phenylamine (**2a**, 30.0 g, 0.14 mol), N-chlorosuccinamide and acetonitrile (1.3 L) was refluxed for 4 hr. The mixture was concentrated under vacuum and the residue was diluted with ethyl acetate (500 mL). The organic layer was washed with water (2X, 250 mL) and brine (250 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent removed under vacuum to give an orange solid residue. Crystallization from ethyl acetate-hexane gave 33.5g (95.3 %) as orange solid, mp 109-110 °C; MS EI *m/e* 250/252/254 ( $M^+$ ).

Elemental analysis for  $C_8H_8Cl_2N_2O_3$ :

Calc'd: C, 38.27; H, 3.21; N, 11.16

Found: C, 38.15; H, 3.10; N, 10.96

#### Example 1

#### [2-(1H-Benzoimidazol-4-yloxy)-ethyl]-benzyl-amine

A solution of 4-(2-chloroethoxy)-benzimidazole (**1**, 0.39 g, 1.98 mmol) and benzylamine (9 mL) was heated at 100 - 110° C for 3.5 hr. The solvent was concentrated under vacuum (50 - 60° C / 0.1 mm), poured into 1 N sodium hydroxide (50 mL) and extracted with ethyl acetate (2X, 50 mL). The combined organic layer was washed with water (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, filtered, and

the solvent removed under vacuum to give 0.58 g of a viscous yellow oil. Purification by chromatography (60 g silica gel, methylene chloride-0.5% 2 M NH<sub>3</sub> in methanol) afforded 0.364 g (68.7 %) of a yellow oil. This material was dissolved in as ethyl acetate-methanol mixture and treated with as excess amount of hydrogen chloride to give the title compound  
5 (0.38 g, 58.5 %) as a white solid, mp 256-259 °C decomposed; MS EI *m/e* 267 (M<sup>+</sup>).

Elemental analysis for C<sub>16</sub>H<sub>17</sub>N<sub>3</sub>O • 2HCl • 0.5H<sub>2</sub>O:

Calc'd: C, 55.02; H, 5.77; N, 12.03

Found: C, 55.26; H, 5.69; N, 12.03

10

### Example 2

#### Benzyl-[2-(2-methyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine

15

A solution of 3-(2-benzylamino-ethoxy)-benzene-1,2-diamine (**4a**, 0.35 g, 1.36 mmol) and acetic acid (10 mL) was refluxed for 14 hr. The solvent was concentrated under vacuum (50 - 60° C / 0.1 mm) and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with 1 N sodium hydroxide (50 mL), water (100 mL) and  
20 brine (100 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent removed under vacuum to give crude base. Purification by chromatography (35 g silica gel, ethyl acetate-1% 2 M NH<sub>3</sub> in methanol) afforded 0.29 g (76.3 %) of pure base as a tan-colored solid foam. This material was dissolved in as ethyl acetate-methanol mixture and treated with as excess amount of 1N hydrogen chloride to give the title compound (0.33 g,  
25 90.0 %) as a white solid, mp >250° C; MS EI *m/e* 281 (M<sup>+</sup>).

Elemental analysis for C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O • 2HCl:

Calc'd: C, 57.63; H, 5.97; N, 11.61

Found: C, 57.23; H, 5.89; N, 12.86

30

## Example 3

## Benzyl-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine

5 A solution of N-[2-(1,2-diamino-benzene-3-yloxy)-ethyl]-N-benzyl-2,2,2-trifluoro-acetamide (6a, 1.0 g, 2.83 mmol) and trifluoroacetic acid (10 mL) was refluxed for 4 hr. The solvent was concentrated under vacuum (50 - 60° C / 0.1 mm) and the residue was dissolved in ethyl acetate (150 mL). The organic layer was washed with 1 N sodium hydroxide (50 mL), water (100 mL) and brine (100 mL), dried over anhydrous  
10 magnesium sulfate, filtered, and the solvent removed under vacuum to give a viscous oil residue<sup>1</sup>. Purification by chromatography (140 g silica gel, ethyl acetate-hexane-2 M NH<sub>3</sub> in methanol (10 : 10 : 1) afforded 0.86 g (70.7 %) of N-benzyl-2,2,2-trifluoro-N-[2-(trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-acetamide as a tan-colored solid foam; MS EI *m/e* 431 (M<sup>+</sup>).

15 A mixture of N-benzyl-2,2,2-trifluoro-N-[2-(trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-acetamide (0.78 g, 1.80 mmol), 6% aqueous methanol (35 mL) and potassium carbonate (1.7 g) was refluxed for 3 hr. The mixture was cooled to 25 °C, poured into water (200 mL) and extracted with ethyl acetate (3X 150 mL). The organic layer was washed with water (200 mL) and brine (200 mL), dried over anhydrous  
20 magnesium sulfate, filtered, and the solvent removed under vacuum to give a solid residue. Crystallization of this material from ethyl acetate afforded 0.50 g (83.5 %) of benzyl-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine • 0.25 ethyl acetate as a white solid, mp 130-131 °C; MS EI *m/e* 335 (M<sup>+</sup>).

25 Elemental analysis for C<sub>17</sub>H<sub>16</sub>F<sub>3</sub>N<sub>3</sub>O • 0.25 C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>:

Calc'd: C, 60.50; H, 5.08; N, 11.76

Found: C, 60.54; H, 4.95; N, 11.72

Benzyl-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine • 0.25 ethyl  
30 acetate (0.40 g, 2.61 mmol) was dissolved in as ethyl acetate-methanol mixture and treated with as excess amount of 1N hydrogen chloride to give the title compound (0.35 g, 79.1 %) as a white solid, mp 194-195 °C; MS EI *m/e* 335 (M<sup>+</sup>).

Elemental analysis for C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O • HCl:

35 Calc'd: C, 57.63; H, 5.97; N, 11.61

Found: C, 57.23; H, 5.89; N, 12.86

## Example 4

**(4-Methyl-benzyl)-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine**

5 The general procedures used in example 2 utilizing 3-[2-(4-methyl-benzylamino)-ethoxy]-benzene-1,2-diamine (4b) and trifluoroacetic acid afforded:

(4-Methyl-benzyl)-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine  
0.25 ethyl acetate as a white solid (60.5 %), mp 154-158 °C; MS EI *m/e* 349 ( $M^+$ ).

10 Elemental analysis for  $C_{18}H_{18}F_3N_3O \cdot 0.25 C_4H_8O_2$ :

Calc'd: C, 61.45; H, 5.43; N, 11.31

Found: C, 61.47; H, 5.40; N, 11.27

15 (4-Methyl-benzyl)-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine dihydrochloride as a white solid (90.1 %), mp 230-233 °C; MS EI *m/e* 349 ( $M^+$ ).

Elemental analysis for  $C_{18}H_{18}F_3N_3O \cdot 2HCl$ :

Calc'd: C, 51.20; H, 4.77; N, 9.95

20 Found: C, 50.92; H, 4.69; N, 9.89

## Example 5

**25 [2-(2-Benzyl-1H-benzoimidazol-4-yloxy)-ethyl]- (4-methyl-benzyl)-amine**

The general procedures used in example 2 utilizing 3-[2-(4-methyl-benzylamino)-ethoxy]-benzene-1,2-diamine (4b) and phenylacetic acid afforded:

30 [2-(2-Benzyl-1H-benzoimidazol-4-yloxy)-ethyl]-(4-methyl-benzyl)-amine dihydrochloride as a white solid (65.8 %), mp >250 °C; MS EI *m/e* 371 ( $M^+$ ).

Elemental analysis for  $C_{24}H_{25}N_3O \cdot 2HCl$ :

Calc'd: C, 64.86; H, 6.12; N, 9.46

35 Found: C, 64.43; H, 6.15; N, 9.31

## Example 6

**(4-Methyl-benzyl)-{2-[2-(1,1,2,2,2-pentafluoro-ethyl)-1H-benzoimidazol-4-yloxy]-ethyl}-amine**

The general procedures used in example 2 utilizing 3-[2-(4-methyl-benzylamino)-ethoxy]-benzene-1,2-diamine (4b) and pentafluoropropionic acid afforded:

(4-Methyl-benzyl)-{2-[2-(1,1,2,2,2-pentafluoro-ethyl)-1H-benzoimidazol-4-yloxy]-ethyl}-amine 1.25 hydrate as a white solid (75.3 %) mp 85-90 °C decomposed; MS EI *m/e* 399 ( $M^+$ ).

Elemental analysis for  $C_{19}H_{18}F_5N_3O \cdot 1.25 H_2O$ :

Calc'd: C, 54.09; H, 4.90; N, 9.96

Found: C, 53.83; H, 4.65; N, 9.76

(4-Methyl-benzyl)-{2-[2-(1,1,2,2,2-pentafluoro-ethyl)-1H-benzoimidazol-4-yloxy]-ethyl}-amine hydrochloride as a white solid (79.7 %) mp 180 °C decomposed; MS EI *m/e* 399 ( $M^+$ ).

Elemental analysis for  $C_{19}H_{18}F_5N_3O \cdot HCl$ :

Calc'd: C, 52.36; H, 4.39; N, 9.64

Found: C, 52.23; H, 4.31; N, 9.54

## Example 7

**Thiophen-2-ylmethyl-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine**

The general procedures used in example 2 utilizing 3-{2-[(thiophen-2-ylmethyl)-amino]-ethoxy}-benzene-1,2-diamine (4c) and trifluoroacetic acid afforded:

Thiophen-2-ylmethyl-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine 1.6 Hydrochloride as a tan solid (58.3 %), mp 184 °C; MS EI *m/e* 341 ( $M^+$ ).

Elemental analysis for  $C_{18}H_{18}F_3N_3O \cdot 1.6HCl$ :

Calc'd: C, 44.98; H, 4.04; N, 10.38

Found: C, 44.99; H, 4.05; N, 10.33

5

### Example 8

#### Benzyl-[3-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-propyl]-amine

The general procedures used in example 2 utilizing 3-(3-benzylamino-propoxy)-  
10 benzene-1,2-diamine (4f) and trifluoroacetic acid afforded:

Benzyl-[3-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-propyl]-amine hemi  
hydrate as a tan solid foam (57.6 %), mp 50-70 °C; MS EI *m/e* 349 (M<sup>+</sup>).

15

Elemental analysis for C<sub>18</sub>H<sub>18</sub>F<sub>3</sub>N<sub>3</sub>O • 0.5 H<sub>2</sub>O:

Calc'd: C, 60.33; H, 5.34; N, 11.73

Found: C, 60.34; H, 5.30; N, 11.84

20

Benzyl-[3-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-propyl]-amine  
Dihydrochloride as a white solid (98.0 %), mp 194-197 °C; MS EI *m/e* 349 (M<sup>+</sup>).

Elemental analysis for C<sub>18</sub>H<sub>18</sub>F<sub>3</sub>N<sub>3</sub>O • 2 HCl:

Calc'd: C, 51.20; H, 4.77; N, 9.95

Found: C, 51.09; H, 4.49; N, 9.86

25

### Example 9

#### Benzyl-{2-[2-(1,1,2,2,2-pentafluoro-ethyl)-1H-benzoimidazol-4-yloxy]- 30 ethyl}-amine

The general procedures used in example 3 utilizing N-[2-(1,2-diamino-benzene-3-  
yloxy)-ethyl]-N-benzyl-2,2,2-trifluoro-acetamide (6a) and pentafluoropropionic acid  
afforded:

35

Benzyl-{2-[2-(1,1,2,2,2-pentafluoro-ethyl)-1H-benzoimidazol-4-yloxy]-ethyl}-  
amine as a white solid (59.8 %), mp 152-153 °C; MS EI *m/e* 385 (M<sup>+</sup>).

Elemental analysis for  $C_{18}H_{16}F_5N_3O$ :

Calc'd: C, 56.11; H, 4.19; N, 10.91

Found: C, 56.02; H, 4.10; N, 10.73

Benzyl-{2-[2-(1,1,2,2,2-pentafluoro-ethyl)-1H-benzoimidazol-4-yloxy]-ethyl}-amine hydrochloride 0.75 hydrate as a white solid (69.4 %), mp 120-135 °C; MS (+)ESI *m/e* 386 ( $M+H^+$ )

Elemental analysis for  $C_{18}H_{16}F_5N_3O \cdot HCl \cdot 0.75 H_2O$ :

Calc'd: C, 49.67; H, 4.28; N, 9.65

Found: C, 49.88; H, 3.95; N, 9.66

#### Example 10

Naphthalen-1-ylmethyl-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine

The general procedures used in example 2 utilizing 3-{2-[(naphthalen-1-ylmethyl)-amino]-ethoxy}-benzene-1,2-diamine (4d) and trifluoroacetic acid afforded:

Naphthalen-1-ylmethyl-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine as a white solid (63.1 %), mp 130-133 °C; MS EI 385 *m/e* ( $M^+$ ).

Elemental analysis for  $C_{21}H_{18}F_3N_3O$ :

Calc'd: C, 65.45; H, 4.71; N, 10.90

Found: C, 65.28; H, 4.43; N, 10.57

Naphthalen-1-ylmethyl-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine hydrochloride as a white solid (94.8 %), mp 208-209 °C; MS EI *m/e* 385 ( $M^+$ ).

Elemental analysis for  $C_{18}H_{18}F_3N_3O \cdot HCl$ :

Calc'd: C, 59.79; H, 4.54; N, 9.96

Found: C, 59.39; H, 4.45; N, 9.81

## Example 11

**Thiophen-2-ylmethyl-[2-(1H-benzoimidazol-4-yloxy)-ethyl]-amine**

The general procedures used in example 2 utilizing 3-[2-[(thiophen-2-ylmethyl)-amino]-ethoxy]-benzene-1,2-diamine (4c) and formic acid afforded:

Thiophen-2-ylmethyl-[2-(1H-benzoimidazol-4-yloxy)-ethyl]-amine quarter hydrate as a viscous yellow oil (63.2 %); MS EI *m/e* 273 ( $M^+$ ).

Elemental analysis for  $C_{14}H_{15}N_3OS \cdot 0.25 H_2O$ :

Calc'd: C, 60.52; H, 5.62; N, 15.12

Found: C, 60.85; H, 5.49; N, 15.39

Thiophen-2-ylmethyl-[2-(1H-benzoimidazol-4-yloxy)-ethyl]-amine dihydrochloride hemihydrate as a white solid (69.2 %), mp 248-252 °C decomposed; MS EI *m/e* 273 ( $M^+$ ).

Elemental analysis for  $C_{14}H_{15}N_3OS \cdot 2.0 HCl \cdot 0.5 H_2O$ :

Calc'd: C, 47.33; H, 5.11; N, 11.83

Found: C, 46.95; H, 5.13; N, 11.73

## Example 12

**(4-Methyl-benzyl)-{2-[2-(1,1,2,2,3,3,3-heptafluoro-propyl)-1H-benzoimidazol-4-yloxy]-ethyl}-amine**

The general procedures used in example 2 utilizing 3-[2-(4-methyl-benzylamino)-ethoxy]-benzene-1,2-diamine (4b) and heptafluorobutyric acid afforded:

(4-Methyl-benzyl)-{2-[2-(1,1,2,2,3,3,3-heptafluoro-propyl)-1H-benzoimidazol-4-yloxy]-ethyl}-amine as a white solid (63.7 %) mp 144-146 °C; MS EI *m/e* 449 ( $M^+$ ).

Elemental analysis for  $C_{20}H_{18}F_7N_3O$ :

Calc'd: C, 53.46; H, 4.04; N, 9.35

Found: C, 53.23; H, 3.69; N, 9.11



5      Elemental analysis for  $C_{19}H_{18}F_5N_3O \cdot 1.5 HCl$ :  
      Calc'd: C, 47.66; H, 3.90; N, 8.34  
      Found: C, 47.47; H, 3.76; N, 8.24

**2-[2-(2-Trifluoromethyl-1H-benzimidazol-4-yloxy-ethyl)-1,2,3,4-tetrahydro-isoquinoline**

2-[2-(2-Trifluoromethyl-1H-benzimidazol-4-yloxy)-ethyl]-1,2,3,4-tetrahydroisoquinoline quarter hydrate as a white solid (95.8 %) mp 168-171 °C; MS EI *m/e* 361 (*M*<sup>+</sup>).

Calc'd: C, 62.37; H, 5.10; N, 11.49  
Found: C, 62.52; H, 4.85; N, 11.50

2-[2-(2-Trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-1,2,3,4-tetrahydroisoquinoline dihydrochloride as a white solid (94.3 %) mp 210-214 °C decomposed; MS EI *m/e* 361 (M<sup>+</sup>).

Calc'd: C, 52.55; H, 4.64; N, 9.68  
Found: C, 52.20; H, 4.81; N, 9.33

## Example 14

**Benzyl-[2-(6-chloro-2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl-amine**

The general procedures used in example 3 utilizing N-benzyl-N-[2-(2,3-diamino-5-chloro-phenoxy)-ethyl]-2,2,2-trifluoro-acetamide (6b) and trifluoroacetic acid afforded:

Benzyl-[2-(6-chloro-2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl-amine as a white solid (76.4 %), mp 171-172 °C; MS EI *m/e* 369 (M<sup>+</sup>).

Elemental analysis for C<sub>17</sub>H<sub>15</sub>ClF<sub>3</sub>N<sub>3</sub>O:

Calc'd: C, 55.22; H, 4.09; N, 11.36

Found: C, 55.05; H, 3.91; N, 11.13

Benzyl-[2-(6-chloro-2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl-amine as a white solid (73.4 %), mp 210-212 °C; MS EI *m/e* 369 (M<sup>+</sup>).

Elemental analysis for C<sub>17</sub>H<sub>15</sub>ClF<sub>3</sub>N<sub>3</sub>O • HCl:

Calc'd: C, 50.26; H, 3.97; N, 10.34

Found: C, 50.29; H, 3.81; N, 10.32

## Example 15

**4-Chloro-benzyl-[2-(6-chloro-2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl-amine**

The general procedures used in example 2 utilizing 3-[2-(4-chloro-benzylamino)-ethoxy]-4-chloro-benzene-1,2-diamine (4g) and trifluoroacetic acid afforded:

4-Chloro-benzyl-[2-(6-chloro-2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl-amine fumarate as a light-gray colored solid (79.6 %), mp 191-193 °C; MS EI *m/e* 403/405/407 (M<sup>+</sup>).

Elemental analysis for C<sub>17</sub>H<sub>14</sub>Cl<sub>3</sub>F<sub>3</sub>N<sub>3</sub>O • C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>:

Calc'd: C, 48.48; H, 3.49; N, 8.08

Found: C, 48.17; H, 3.26; N, 8.11

## Example 16

**(4-Fluoro-benzyl)-2[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine**

The general procedures used in example 2 utilizing 3-[2-(4-fluoro-benzylamino)-ethoxy]-benzene-1,2-diamine (4h) and trifluoroacetic acid afforded:

(4-Fluoro-benzyl)-2[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine hydrochloride hemihydrate as a white solid (50.4 %), mp 225-227 °C; MS EI *m/e* 353(M<sup>+</sup>).

Elemental analysis for C<sub>17</sub>H<sub>15</sub>F<sub>4</sub>N<sub>3</sub>O•1.0 HCl•0.5 H<sub>2</sub>O:

Calc'd: C, 51.20; H, 4.30; N, 10.54

Found: C, 51.06; H, 3.93; N, 10.35

## Example 17

**[2-(2-Trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-(4-trifluoromethyl-benzyl)-amine**

The general procedures used in example 2 utilizing 3-[2-(4-trifluoromethyl-benzylamino)-ethoxy]-benzene-1,2-diamine (4i) and trifluoroacetic acid afforded:

[2-(2-Trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-(4-trifluoromethyl-benzyl)-amine hydrochloride as a white solid (80.5 %), mp 188-190 °C; MS (+)FAB *m/e* 404 (M+H<sup>+</sup>).

Elemental analysis for C<sub>18</sub>H<sub>15</sub>F<sub>6</sub>N<sub>3</sub>O•1.0 HCl:

Calc'd: C, 49.16; H, 3.67; N, 9.55

Found: C, 49.21; H, 3.50; N, 9.46

## Example 18

**(3-Phenyl-propyl)-[2-(2-trifluoromethyl-1H-benzimidazol-4-yloxy)-ethyl]-amine**

5 The general procedures used in example 2 utilizing 3-[2-(3-phenyl-propylamino)-ethoxy]-benzene-1,2-diamine (4j) and trifluoroacetic acid afforded:

(3-Phenyl-propyl)-[2-(2-trifluoromethyl-1H-benzimidazol-4-yloxy)-ethyl]-amine hydrochloride as a white solid (88.7 %), mp 167-170 °C; MS (+)FAB *m/e* 364 (M+H<sup>+</sup>).

10 Elemental analysis for C<sub>19</sub>H<sub>20</sub>F<sub>3</sub>N<sub>3</sub>O 1.0 HCl:

Calc'd: C, 57.07; H, 5.29; N, 10.51

Found: C, 56.89; H, 5.15; N, 10.28

## 15 PHARMACOLOGY

The compounds of this invention are dopamine autoreceptor agonists, that is, they serve to modulate the synthesis and release of the neurotransmitter dopamine. They are thus useful for treatment of disorders of the dopaminergic system, such as schizophrenia, 20 Parkinson's disease and Tourette's syndrome. Such agents are partial agonists at the postsynaptic dopamine D<sub>2</sub> receptor and are thereby useful in the treatment of alcohol and drug addiction.

Affinity for the dopamine autoreceptor was established by a modification of the 25 standard experimental test procedure of Seemen and Schaus, European Journal of Pharmacology 203: 105-109, 1991, wherein homogenized rat striatal brain tissue is incubated with <sup>3</sup>H-quinpirole (Quin.) and various concentrations of test compound, filtered and washed and counted in a Betaplate scintillation counter.

30 High affinity for the dopamine D-2 receptor was established by the standard experimental test procedure of Fields, et al., Brain Res., 136, 578 (1977) and Yamamura et al., eds., Neurotransmitter Receptor Binding, Raven Press, N.Y. (1978) wherein homogenized limbic brain tissue is incubated with <sup>3</sup>H-spiroperidol (Spiper.) and various concentrations of test compound, filtered and washed and shaken with Hydrofluor 35 scintillation cocktail (National Diagnostics) and counted in a Packard 460 CD scintillation counter.

The results of the tests with compounds representative of this invention are given in the immediately following table.

Example No.	IC <sub>50</sub> (nM) D <sub>2</sub> Quin.	IC <sub>50</sub> (nM) D <sub>2</sub> Spiper	Ratio
1	26.75	--	--
2	8.85	339	38.3
3	0.36	23.7	65.8
4	0.74	29.9	40.4
5	54.8	2159	39.4
6	1.44	66.5	46.2
7	1.03	37.35	36.3
8	86.76	1456	16.8
9	1.41	41.88	29.7
10	0.86	81.5	94.8
11	52.8	--	--
12	5.12	118.0	23.0
13	8.00	314.4	39.4
14	1.42	150.5	106
15)	7.77	395.0	50.8
16	0.74	49.0	66.2
17	1.16	87.0	75.0
18	0.56	--	--

5

Hence, the compounds of this invention effect the synthesis of the neurotransmitter dopamine and thus are useful in the treatment of dopaminergic disorders such as schizophrenia, Parkinson's disease, Tourette's Syndrome, alcohol addiction, cocaine addiction, and addiction to analagous drugs.

10

Applicable solid carriers for pharmaceutical compositions containing the compounds of this invention can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary

compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl  
5 cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of  
10 both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g.  
15 cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

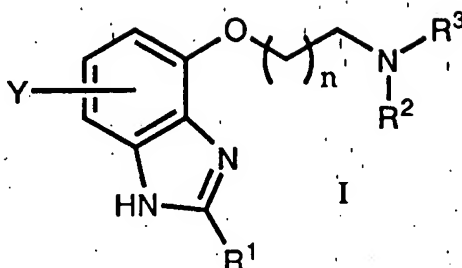
20  
Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

25  
Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing  
30 liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The dosage to be used in the treatment of a specific psychosis must be subjectively determined by the attending physician. The variables involved include the specific  
35 psychosis and the size, age and response pattern of the patient.

## WHAT IS CLAIMED IS:

(1) A compounds of formula I:



wherein:

R<sup>1</sup> is hydrogen, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, straight-chain or branched alkyl group having up to 6 carbons or benzyl optionally substituted by one to three substituents selected from halogen, amino, nitro, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy;

R<sup>2</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl.

R<sup>3</sup> is hydrogen, straight-chain or branched alkyl group having up to 10 carbon atoms, cyclohexylmethyl, -(CH<sub>2</sub>)<sub>m</sub>Ar where Ar is phenyl, thienyl, furanyl, or pyridinyl, each optionally substituted by one to two substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkoxy, trifluoromethyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

or NR<sup>2</sup>R<sup>3</sup> is 1,2,3,4-tetrahydroquinolin-1-yl or 1,2,3,4-tetrahydroisoquinolin-2-yl;

Y = halogen, lower alkyl, amino, and lower alkoxy;

n = 1-5;

or a pharmaceutically acceptable salt thereof.

(2) A compound according to claim 1 wherein R<sup>2</sup> is benzyl, substituted benzyl, thienylmethyl, tetrahydroisoquinoline, furanylmethyl, phenylbutyl, cyclohexylmethyl, or 4-fluorobutyrophenone and R<sup>1</sup> is trifluoromethyl or tetrafluoroethyl.

(3) A compound according to claim 1 which is [2-(1H-benzoimidazol-4-yloxy)-ethyl]-benzyl-amine or a pharmaceutically acceptable salt thereof.

(4) A compound according to claim 1 which is benzyl-[2-(2-methyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine or a pharmaceutically acceptable salt thereof.

(5) A compound according to claim 1 which is benzyl-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine or a pharmaceutically acceptable salt thereof.

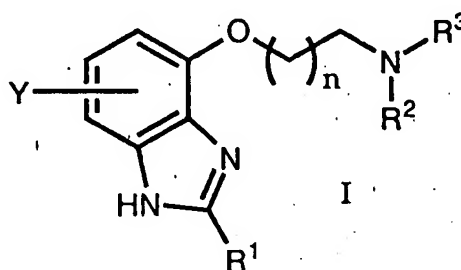
- (6) A compound according to claim 1 which is (4-methyl-benzyl)-[2-(2-trifluoromethyl-1H-benzimidazol-4-yloxy)-ethyl]-amine or a pharmaceutically acceptable salt thereof.
- (7) A compound according to claim 1 which is [2-(2-benzyl-1H-benzimidazol-4-yloxy)-ethyl]- (4-methyl-benzyl)-amine or a pharmaceutically acceptable salt thereof.
- (8) A compound according to claim 1 which is (4-methyl-benzyl)-{2-[2-(1,1,2,2,2-pentafluoro-ethyl)-1H-benzimidazol-4-yloxy]-ethyl}-amine or a pharmaceutically acceptable salt thereof.
- (9) A compound according to claim 1 which is thiophen-2-ylmethyl-[2-(2-trifluoromethyl-1H-benzimidazol-4-yloxy)-ethyl]-amine or a pharmaceutically acceptable salt thereof.
- (10) A compound according to claim 1 which is benzyl-[3-(2-trifluoromethyl-1H-benzimidazol-4-yloxy)-propyl]-amine or a pharmaceutically acceptable salt thereof.
- (11) A compound according to claim 1 which is benzyl-{2-[2-(1,1,2,2,2-pentafluoro-ethyl)-1H-benzimidazol-4-yloxy]-ethyl}-amine or a pharmaceutically acceptable salt thereof.
- (12) A compound according to claim 1 which is nNaphthalen-1-ylmethyl-[2-(2-trifluoromethyl-1H-benzimidazol-4-yloxy)-ethyl]-amine or a pharmaceutically acceptable salt thereof.
- (13) A compound according to claim 1 which is thiophen-2-ylmethyl-[2-(1H-benzimidazol-4-yloxy)-ethyl]-amine or a pharmaceutically acceptable salt thereof.
- (14) A compound according to claim 1 which is (4-methyl-benzyl)-{2-[2-(1,1,2,2,3,3,3-heptafluoro-propyl)-1H-benzimidazol-4-yloxy]-ethyl}-amine or a pharmaceutically acceptable salt thereof.
- (15) A compound according to claim 1 which is 2-[2-(2-trifluoromethyl-1H-benzimidazol-4-yloxy-ethyl)-1,2,3,4-tetrahydro-isoquinoline or a pharmaceutically acceptable salt thereof.
- (16) A compound according to claim 1 which is benzyl-[2-(6-chloro-2-trifluoromethyl-1H-benzimidazol-4-yloxy)-ethyl]-amine or a pharmaceutically acceptable salt thereof.
- (17) A compound according to claim 1 which is 4-chloro-benzyl-[2-(6-chloro-2-trifluoromethyl-1H-benzimidazol-4-yloxy)-ethyl]-amine or a pharmaceutically acceptable salt thereof.
- (18) A compound according to claim 1 which is (4-fluoro-benzyl)-2[2-(2-trifluoromethyl-1H-benzimidazol-4-yloxy)-ethyl]-amine or a pharmaceutically acceptable salt thereof.



(19) A compound according to claim 1 which is [2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-(4-trifluoromethyl-benzyl)-amine or a pharmaceutically acceptable salt thereof.

(20) A compound according to claim 1 which is (3-phenyl-propyl)-[2-(2-trifluoromethyl-1H-benzoimidazol-4-yloxy)-ethyl]-amine or a pharmaceutically acceptable salt thereof.

(21) A method of treating diseases in a mammal which respond to treatment with dopamine D<sub>2</sub> agonists which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of the formula



wherein:

R<sup>1</sup> is hydrogen, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, straight-chain or branched alkyl group having up to 6 carbons or benzyl optionally substituted by one to three substituents selected from halogen, amino, nitro, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy and C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl.

R<sup>3</sup> is hydrogen, straight-chain or branched alkyl group having up to 10 carbon atoms, cyclohexylmethyl, -(CH<sub>2</sub>)<sub>m</sub>Ar where Ar is phenyl, thienyl, furanyl, or pyridinyl, each optionally substituted by one to two substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkoxy, trifluoromethyl or C<sub>1</sub>-C<sub>6</sub> alkyl;

or NR<sup>2</sup>R<sup>3</sup> is 1,2,3,4-tetrahydroquinolin-1-yl or 1,2,3,4-tetrahydroisoquinolin-2-yl;

Y = halogen, lower alkyl, amino, and lower alkoxy;

n = 1-5;

or a pharmaceutically acceptable salt thereof.

(22) The method of treatment according to claim 21 wherein the disease treated is schizophrenia.

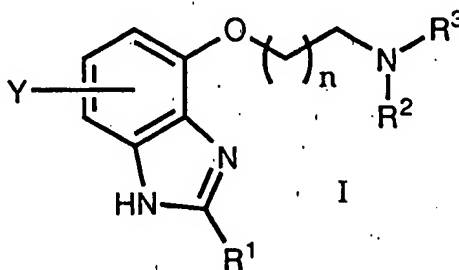
(23) The method of treatment according to claim 21 wherein the disease treated is Parkinson's disease.

(24) The method of treatment according to claim 21 wherein the disease treated is Tourette's syndrome.

5 (25) The method of treatment according to claim 21 wherein the disease treated is drug or alcohol addiction.

(26) A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the formula

10



wherein:

15  $R^1$  is hydrogen, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, straight-chain or branched alkyl group having up to 6 carbons or benzyl optionally substituted by one to three substituents selected from halogen, amino, nitro, hydroxy,  $C_1-C_6$  alkoxy;

$R^2$  is hydrogen or  $C_1-C_6$  alkyl.

20  $R^3$  is hydrogen, straight-chain or branched alkyl group having up to 10 carbon atoms, cyclohexylmethyl,  $-(CH_2)_mAr$  where Ar is phenyl, thienyl, furanyl, or pyridinyl, each optionally substituted by one to two substituents selected from halogen,  $C_1-C_6$  alkoxy, trifluoromethyl or  $C_1-C_6$  alkyl;

or  $NR^2R^3$  is 1,2,3,4-tetrahydroquinolin-1-yl or 1,2,3,4-tetrahydroisoquinolin-2-yl;

25 Y = halogen, lower alkyl, amino, and lower alkoxy;

n = 1-5;

or a pharmaceutically acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 98/00613

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D235/06 A61K31/415 C07D235/08 C07D235/10 C07D409/12  
C07D401/12 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JAEN J.C. ET AL.: "Dopamine autoreceptor agonists as potential antipsychotics. 1. (Aminoalkoxy)anilines" JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 8, August 1988, pages 1621-1625, XP000674393 see the whole document	1-20, 26
Y	EP 0 237 781 A (WARNER-LAMBERT COMPANY) 23 September 1987 see claims 1,7	1-20, 26
Y	EP 0 707 007 A (MERCK PATENT GMBH) 17 April 1996 see page 3, line 2 - line 3; claims 1,9	1-20, 26
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

13 May 1998

Date of mailing of the international search report

23.06.98

Name and mailing address of the ISA

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Authorized officer

Hartrampf, G

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/00613

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 97 23216 A (WARNER-LAMBERT COMPANY & COCENSYS, INC. ) 3 July 1997 see claims 1-3, 7-9, 36 -----	1-20, 26
E	WO 98 08817 A (AMERICAN HOME PRODUCTS CORPORATION) 5 March 1998 see the whole document -----	1-20, 26

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 00613

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 21-25  
because they relate to subject matter not required to be searched by this Authority, namely:  
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/00613

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 237781 A	23-09-87	US 4704390 A CA 1280750 A JP 62252783 A US 4803203 A	03-11-87 26-02-91 04-11-87 07-02-89
EP 707007 A	17-04-96	AU 3421895 A BR 9504379 A CA 2160447 A CN 1130180 A CZ 9502661 A FI 954874 A HU 75644 A JP 8225501 A NO 954080 A PL 310932 A SK 126695 A ZA 9508673 A	26-04-96 27-05-97 15-04-96 04-09-96 17-04-96 15-04-96 28-05-97 03-09-96 15-04-96 15-04-96 05-06-96 22-05-96
WO 9723216 A	03-07-97	AU 1689997 A	17-07-97
WO 9808817 A	05-03-98	NONE	